THE DRUG PROBLEM IN PREGNANCY

VIRGINIA APGAR, M.D., M.P.H.

From the National Foundation—March of Dimes, New York City

SINCE THE UNFORTUNATE THALIDOMIDE episode of 1959–1962, there has been an "epidemic" of papers relating to the fetal effects of drugs taken by or given to a pregnant woman in the first trimester. By fetal effects is meant the teratogenic action of such drugs, which is of importance only to the tenth or eleventh week of pregnancy, or the pathologic effects on a normally developed fetus after eleven weeks of age even to the point of death. There may well be pathologic effects on the fetus during the first eleven weeks that do not interfere with normal organogenesis, but little is known about them.

One important change in thinking has taken place in the past decade. The idea that the placenta is a barrier to the transfer of drugs from the mother to the fetus has been disproved. Rather, the placenta is a sieve. Almost everything ingested by or injected into the mother can be expected to reach the fetus in a few minutes. A high molecular weight does not interfere with transmission to the fetus, except for a time lag of a few minutes.

Drugs can be and are ingested or injected at any time during pregnancy. Peckham and King report that such is the case with prescribed drugs in 92 per cent of pregnancies. Almost no studies have been made on the use of "over-the-counter" drugs by pregnant women. (This was done for a time in the Fetal Life Study when Dr. Gilbert Mellin took over its direction, but it was discontinued in 1959.)

THALIDOMIDE AND ITS EFFECTS

There is not one instance of complete agreement about the teratogenic effects on the human fetus of a drug given to the mother during the first trimester. By far the best example of nearly complete agreement is the association of the ingestion of thalidomide and the appearance of phocomelia in the fetus (as well as several other anomalies). From the reports in over a hundred papers, the connection between the ingestion of thalidomide and the appearance of specific abnormalities in the infants appears to be close. Yet, in an extensive monograph by Sievers, thalidomide is exonerated from any

such association. No attempt is made here to specify at what point in the pregnancy the drug was ingested or to connect it with given abnormalities, for as Lenz has pointed out, most reports do not distinguish between the day of ingestion after the last menstrual period or after the day of conception, when known—if indeed it is. McBride's early paper (1961) is remarkable in that the day of conception is specified in every case. Dr. McBride should be recognized as among the first, if not indeed the first, to associate ingestion of thalidomide with the appearance of congenital anomalies.

In view of the importance of the genetic background of the parents in any teratogenic problem, it is interesting to note that there is no agreement about this aspect of the thalidomide problem. In general, it has been stated that about 20 per cent of the women who ingested thalidomide, in any of its 60 or so combinations, gave birth to abnormal babies. Lenz strongly disagrees with this figure; he believes that *every* woman who took the drug during the critical period of organogenesis of the skeletal and gastrointestinal tracts was delivered of an abnormal baby. He has canvassed the medical profession in Europe, the United States, and Australia in an attempt to find cases that do not fit this theory. At the time of this writing, there were possibly 3 women whose histories did not fit the 100 per cent concept, but there is some doubt about the actual time of ingestion of the drug in these women.

It is a bit disturbing that in two different areas, phocomelia occurred more frequently in 1965 than it did in prethalidomide days. Here, the problem of record-keeping and registries arises. Incidence and prevalence rates for phocomelia before 1960 do not exist. Phocomelia is not new; every crippled children's clinic has had a small number of such patients for years. In Nova Scotia, a rehabilitation specialist, Dr. Gingras, recently stated that he was receiving more of these patients than usual for treatment, despite the fact that thalidomide has been removed from the market for some time. It is possible that the drug was retained in the family's or a neighbor's medicine cabinet and used for sedation by the pregnant woman. Dr. Harry Medovy, in Winnipeg disagrees with the idea that the level of new phocomelic patients is elevated at present.

Dr. Arthur Robinson, Director of The National Foundation—March of Dimes Birth Defects Center in Denver, told me recently that they have noted a somewhat increased number of new patients with phocomelia, in whom the ingestion of thalidomide apparently was not a factor.

These reports serve to put into focus the great need for base-line

data. How many birth defects, rigorously defined and classified, occur in what base-line population? How can one tell whether congenital anomalies in general, or specific ones, are increasing or decreasing? One of the few papers on this subject is by Gittelsohn and Milham, and concerns the incidence (new births) of babies with anencephalia, hydrocephalia, and/or spina bifida diagnosed at birth. It is encouraging that they found that 90 per cent of the diagnoses were accurate on the birth certificates. In New York State (excluding New York City) over a 15-year observation period, they found the rate for these anomalies to be decreasing.

The observation of Hellmann *et al.* that administration of thalidomide before or during the period of skin grafting in rabbits slightly increased their immunologic tolerance is an intriguing one. Their belief that many of the babies born with the typical thalidomide deformities would have been aborted had the drug not been ingested cannot be confirmed. I personally doubt it, for in the few clinics where attention is paid to autopsies of abortion specimens, phocomelia is a most unusual observation. At this point, one should note that the uncertainties described above relate to the one drug on which there is the greatest agreement as to its teratogenic action in man.

OTHER DRUGS

There are three drugs, or groups of drugs, that should be discussed, about which there is much greater disagreement as to their teratogenic effect in man. At the time of this writing (March, 1966), there is much discussion about the Food and Drug Administration's stipulation that meclizine, cyclizine, and chlorcyclizine must bear labeling calling attention to the "danger of birth deformities if the drugs are taken by pregnant women" (*The New York Times,* March 5, 1966). The caution reflected in the label comes entirely from experimental teratology in species other than man. At the moment, there is no evidence in two studies on pregnant women that these drugs have any teratogenic action.[23, 39]

In most of the hundreds of papers on experimental teratogenesis in animals, caution is recommended in transferring the results to the human species. Indeed, if we did consider all species equal in this respect, we should not be drinking coffee, taking an aspirin, or accepting cortisone or insulin as medication. These substances are teratogenic in certain strains of mice or chick embryos. Although it is unlikely that these common substances are teratogenic for human beings, data do not exist to prove or disprove this idea.

Cytotoxic Drugs

Cytotoxic drugs have been used during pregnancy for two purposes—abortion and treatment of leukemia or Hodgkin's disease. Aminopterin, a folic acid antagonist, has been used with signal success by Thiersch for therapeutic abortion of pregnant women with active tuberculosis. His series is small but carefully documented. Of 24 patients receiving the drug, 16 had successful spontaneous abortions. Of the 8 remaining women, aborted therapeutically with dilation and curettage, the pregnancies in 4 were grossly abnormal. The photograph of one infant who survived Aminopterin treatment of its mother is shown repeatedly at pediatric, obstetric, and teratologic meetings; it was grossly abnormal.

It is well known from experiments in animals that agents designed to interfere with abnormal cell division, such as those used in Hodgkin's disease and leukemia, may cause congenital abnormalities in the fetus when pregnancy occurs during the course of the illness.[14, 15] There are several useful reviews of the effects of cytotoxic agents given to women with Hodgkin's disease or leukemia who also became or were pregnant.[3, 18, 24, 32, 33] Apparently, pregnancy does not affect these two conditions adversely. It is strongly recommended that cytotoxic drugs not be administered during the first three months of pregnancy because of their possible teratogenic effects.

Cortisone

Cortisone and its pharmacologic relatives are administered for a variety of human ailments. In special strains of mice, cleft palate can be induced in 100 per cent of the litter by judicious administration of a large dose of cortisone to the mother at a certain date in pregnancy. There is, to date, no controlled human experience with the use of this drug in early pregnancy, i.e., 5–6 weeks after conception.[2, 28] Two reports, without controls, indicate an incidence of 8.5 per cent[5] and 2.3 per cent[11] of cleft-palate offspring from mothers who were being treated with cortisone. However, no genetic histories are available, and they are most necessary for interpretation of data concerning this anomaly. Moreover, the total number of infants covered by these studies is only 28. It is hoped that the collaborative study being conducted by the National Institute of Neurological Diseases and Blindness, which includes 50,000 pregnancies, will provide further information on this association. Only one-third of the mothers entering the study were in the first trimester. However,

this group represents the largest number of pregnant women so studied, and the records on each pregnancy are voluminous.

Progestins

Special attention should be given to the problem of masculinization of a few female infants whose mothers were given synthetic progestins toward the end of the first trimester. This is not really an example of teratogenesis, but of overgrowth of the phallus and fusion of the labia which were already normally formed. In 1958, Hayles and Nolan, Wilkins,[37, 38] and Moncrieff described this syndrome. Wilkins first observed this association in a week-old girl born in 1950. Differentiation of the genitourinary tract occurs relatively late in the timetable of human organogenesis. Between the tenth and eleventh week after conception, anatomic sex becomes definitive, and the various parts of the kidney have finally joined.[4, 16] In one case in Wilkins' report, 17-a-ethinyltestosterone was started in the fourteenth week of gestation and in another, in the sixteenth week. Enlargement of the phallus occurred in both infants. The use of these drugs leads to definite fetal changes, but they are not properly teratogenic drugs.

There are many effects of drugs on the fetus other than teratogenic ones. Deposit of tetracycline in bones and teeth, hyperbilirubinemia, anemia, ileus, and fetal vaccinia are examples of pathologic changes in the fetus as a result of drug administration after organogenesis has been completed. In the reviews of McKay and Lucey, Cohlan, Lucey, and Warkany and Kalter, the subject is broadly discussed.

FUTURE STUDY

What direction should the study of human teratogenesis take? This study is a serious challenge, but one that must be met. Two lines of action seem indicated. First, there must be some kind of a registry of birth defects on a nationwide, state, or county level. Some governmental subdivision is desirable, for its is necessary to have base-line population data to compute incidence and prevalence figures. Until such a registry is established, there is no way to know whether birth defects are increasing or decreasing, or whether a cluster of defects is significant or not. To date, British Columbia has the most complete registry in this hemisphere.[29] Greene *et al.*, concentrating on cleft lip and palate, have made an excellent start in certain well-defined areas in this country.

Second, there must be a truly prospective study of women in early pregnancy with regard to drug intake. Evans is somewhat discouraging about the likelihood of success. Pregnancy must be recognized early, with biweekly pregnancy tests of women who are trying to become pregnant. Present immunochemical tests can determine pregnancy 19 days after conception, and often earlier. A likely group with which to begin such a study would be the wives of interns and residents. Informal inquiry shows that motivation in this group would be excellent.

As soon as pregnancy is recognized, or even before, a prospective pregnancy health history would be kept by the mother for the first 12–16 weeks, or even before established pregnancy. Anything beyond the normal intake of food would be recorded daily and the record collected weekly. Once the method was firmly established, many other prenatal influences could be recorded; emotional state, trauma, frequency of intercourse, and unusual exposure to other environmental factors could thus be related to the outcome of pregnancy. The data would be recorded and stored by a computer and a copy sent to the obstetrician if he wished. Stable data, such as blood groups and Rh factor of each parent, family history for birth defects, occupation of the husband, education of each parent, and address and social security number of both parents, etc., could be included from the physician's records and collated.

The result of the pregnancy would be recorded in all of the women under study, and examination of their infants extended to at least one year. McIntosh *et al.* found that 97.3 per cent of birth defects were diagnosable at one year of age, while Wallace and Saunders found that this figure was 84 per cent. With the newer, broader view of "birth defects," one year may be too short a follow-up period. Certain metabolic disorders and some forms of mental retardation become expressed in the preschool years and even later.

Obviously, the pilot group for this study would be extremely biased in favor of high intelligence, planned pregnancy, and interest in human teratogenesis. After the problems have been cleared from this select group, the study could be scaled down to usefulness in less privileged groups with different language orientation and different economic conditions.

I am convinced that such studies can be made, but it is imperative that we have the cooperation of obstetricians and pediatricians, as well as general practitioners who are truly in the best position to recognize environmental and genetic effects in their patients of reproductive age. "To study mankind, study man."[1]

REFERENCES

1. BARTLETT, J. *Familiar Quotations*, Ed. 13. Little, Brown, Boston, 1955, pp. 316b, 60a.
2. BONGIOVANNI, A. M., and MCPADDEN, A. J. Steroids during pregnancy and possible fetal consequences. *Fertil. and Steril. 2:*181, 1960.
3. COHLAN, S. Q. Fetal and neonatal hazards from drugs administered during pregnancy. *N. Y. St. J. Med. 64:*493, 1964.
4. DAVIES, J. *Human Developmental Anatomy.* Ronald, New York, 1963.
5. DOIG, R. K., and COLTMAN, O. M. Cleft palate following cortisone therapy in early pregnancy. *Lancet* 2:730, 1956.
6. EVANS, T. Personal communication, November 12, 1965.
7. FLOERSHEIM, G. L. Another chance for thalidomide. *Lancet 1:*207, 1966.
8. GINGRAS, G. *Medical Tribune,* July 21, 1965.
9. GITTELSOHN, A. M., and MI'HAM, S. Declining incidence of central nervous system anomalies in New York State. *Brit. J. prev. soc. Med. 16:*153, 1962.
10. GREENE, J. A., VERMILLION, J. R., and HAY, S. Utilization of birth certificates in epidemiological studies of cleft lip and palate. Presented at American Public Health Association meeting, October 7, 1964.
11. HARRIS, J. W. S., and ROSS, I. P. Cortisone therapy in early pregnancy. *Lancet 1:*1045, 1956.
12. HAYLES, A. B., and NOLAN, R. B. Masculinization of female fetus possibly related to administration of progesterone during pregnancy: Report of two cases. *Proc. Mayo Clin. 33:*200, 1958.
13. HELLMANN, K., DUKE, D. I., and TUCKER, D. F. Prolongation of skin homograft survival by thalidomide. *Brit. med. J. 2:*687, 1965.
14. KALTER, H., and WARKANY, J. Experimental production of congenital malformations in mammals by metabolic procedure. *Physiol. Rev. 39:*69, 1959.
15. KARNOFSKY, D., and CLARKSON, B. D. Cellular effects of anticancer drugs. *Ann. Rev. Pharmacol. 3:*357, 1963.
16. LANGMAN, J. *Medical Embryology.* Williams & Wilkins, Baltimore, 1963.
17. LENZ, W. Personal communication, 1965.
18. LUCEY, J. F. Drugs and the intra-uterine patient. Symposium on the Placenta. March 6, 1964. Birth Defects Original Article Series #1, The National Foundation, April 1965.
19. MCBRIDE, W. G. Thalidomide and congenital anomalies. *Lancet* 2:1358, 1961.
20. MCBRIDE, W. G. Drugs and foetal abnormalities. *Brit. med. J.* 532:1681, 1962.
21. MCINTOSH, R., MERRITT, K. K., RICHARDS, M. R., SAMUELS, M. H., and BELLOWS, M. T. Incidence of congenital malformations: Study of 5964 pregnancies. *Pediatrics 14:*505, 1954.

22. McKay, R. J., Jr., and Lucey, J. F. Neonatology. *New Engl. J. Med. 270*:1231; 1292, 1964.
23. Mellin, G. W., and Katzenstein, M. Meclizine and fetal abnormalities. *Lancet 1*:222, 1963.
24. Meltzer, H. J. Congenital anomalies due to attempted abortion with 4-aminopteroglutamic acid. *J. Amer. med. Ass. 161*:1253, 1956.
25. Moncrieff, A. Nonadrenal female pseudohermaphroditism associated with hormonal administration in pregnancy. *Lancet 2*:267, 1958.
26. Neel, J. V. Some genetic aspects of congenital defects. First International Conference on Congenital Malformations. Lippincott, Philadelphia, 1961.
27. Peckham, C. H., and King, R. W. Study of intercurrent conditions observed during pregnancy. *Amer. J. Obstet. Gynec. 87*:609, 1963.
28. Popert, A. J. Pregnancy and adrenal cortical hormones. *Brit. med. J. 1*:967, 1962.
29. Registry for handicapped children and adults: *Annual Report 1962.* Division of Vital Statistics: Special Report No. 77, Health Branch, Department of Health Services and Hospital Insurance. British Columbia.
30. Shotton, D., and Monie, I. W. Possible teratogenic effect of chlorambucil on a human fetus. *J. Amer. med. Ass. 188*:74, 1963.
31. Sievers, G. Clinical-statistical studies of the topical problem of congenital abnormalities. *Arzneimittel-Forsch. 14*:605, 1964.
32. Smith, R. B. W., Sheehy, T. W., and Rothberg, H. Hodgkin's disease and pregnancy. *Arch. Inst. Med. 102*:777, 1958.
33. Sokal, J. E., and Lessman, E. M. Effects of cancer chemotherapeutic agents on the human fetus. *J. Amer. med. Ass. 172*:1765, 1960.
34. Thiersch, J. B. Therapeutic abortion with a folic acid antagonist administered by the oral route. *Amer. J. Obstet. Gynec. 63*:1298, 1952.
35. Wallace, H., and Sanders, D. Mortality experience in children with congenital malformations. *J. Pediat. 54*:801, 1959.
36. Warkany, J., and Kalter, H. Congenital malformations. *New Engl. J. Med. 265*:993; 1046, 1961.
37. Wilkins, L. Masculinization of the female fetus due to use of orally-given progestins. *J. Amer. med. Ass. 172*:1028, 1960.
38. Wilkins, L., Jones, H. W., Holman, G. H., and Stempfel, R. S. Masculinization of female fetus associated with administration of oral and intramuscular progestins during gestation: Nonadrenal female pseudohermaphroditism. *J. clin. Endocr. 18*:559, 1958.
39. Yerushalmy, J., and Milkovich, L. Evaluation of the teratogenic effect of meclizine in man. *Amer. J. Obstet. Gynec. 93*:553, 1965.